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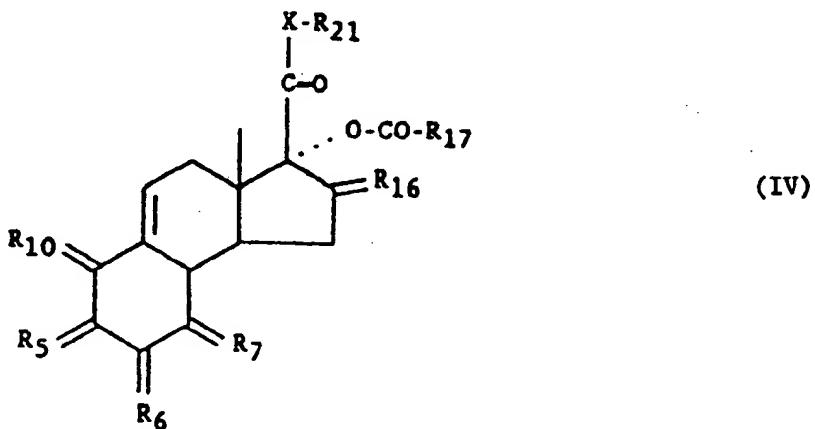
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(54) Title: SURAMIN TYPE COMPOUNDS AND ANGIOSTATIC STEROIDS TO INHIBIT ANGIOGENESIS



(57) Abstract

The invention is a method of treating angiogenesis in a warm blooded mammal who is in need of such treatment which comprises administration of an angiogenic inhibiting amount of a combination of a suramin-type compound and an angiostatic steroid. Angiostatic steroids include the known 20-substituted steroids of formula (I), 21-hydroxy steroids of formula (II), C₁₁-functionalized steroids of formula (III) as well as the novel $\Delta^{9(11)}$ -etianic esters of formula (IV), as well as various individual known steroids.

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SURAMIN TYPE COMPOUNDS AND ANGIOSTATIC STEROIDS TO
INHIBIT ANGIOGENESIS

BACKGROUND OF THE INVENTION

1. Field of the Invention

5 The present invention is a method of treating angiogenesis in mammals who have a need for the same which utilizes suramin or suramin-type compounds and an angiostatic steroid. Conditions in which this combination may be used are diseases of neovascularization such as cancer, diabetes and arthritis.

10 2. Description of the Related Art

Angiogenesis is the development of blood vessels which typically would lead to a vascular bed capable of sustaining viable tissue. Angiogenesis is a necessary process in the establishment of embryonic tissue and development of a viable embryo. Similarly, angiogenesis 15 is a necessary step in the establishment and development of tumor tissue as well as certain inflammatory conditions. The inhibition of angiogenesis would be useful in the control of embryogenesis, inflammatory conditions, and tumor growth, as well as numerous other conditions.

20 European patent application No 83870132.4 (Publication No 0 114 589) published August 1, 1984 describes the use of cortisone, hydrocortisone and 11 α -hydrocortisone in combination with heparin in the inhibition of angiogenesis.

25 The angiogenesis inhibitory effects of heparin and heparin fragments in combination with cortisone is described in Science 221, 719 (1983). The use of heparin and heparin fragments in combination with hydrocortisone is set forth in the Proceedings of AACR 26, 384 (1985).

30 Heparin is presently used with inhibitors of angiogenesis, especially angiostatic steroids to treat diseases involving neovascularization, see Biochem. Pharmacol. 34, 905 (1985) and Annals of Surgery 206, 374 (1987). The heparin potentiates the angiogenesis-inhibiting activity of other drugs, for example of collagen biosynthesis inhibitors such as L-azetidine carboxylic acid. The 35 problem with using heparin is that the efficacy of each preparation/batch of heparin differs due to the chemical heterogeneity of the heparin molecules.

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β -Cyclodextrin tetradecasulfate is known to be a substitute for heparin in anti-angiogenesis treatments containing angiostatic steroids, see Science 243, 1490 (1989).

Suramin inhibits the binding of fibroblast growth factor to its receptor during *in vitro* experiments. Fibroblast growth factor is one of a number of known angiogenic growth factors. See, J. Cell Physiol. 132, 143 (1987).

Suramin and 4,4'-bis[[4-(*o*-hydroxyanilino)-6-(*m*-sulfoanilino)-*s*-triazin-2-yl]amino]-2,2'stilbenedisulfonic acid have been reported to possess antitumor activity. See, Gann 61, 569 (1970) and J. Clin. Oncol., 7, 499 (1989).

US Patent 4,599,331 discloses 20-substituted $\Delta^{1,4}$ -16-methyl steroids which did not have a $\Delta^9(11)$ double bond which are useful as antiangiogenics.

US Patent 4,771,042 discloses 21-hydroxy steroids which are useful in the inhibition of angiogenesis involving the co-administration of steroids with heparin or heparin fragments.

International Patent Publication WO87/02672 discloses various C_{11} -functionalized steroids useful in the inhibition of angiogenesis.

The Journal of the National Cancer Institute 81, 1346 (1989) discloses that "Suramin also appears to have antiangiogenesis activity ...".

The combination of suramin-type compounds and angiostatic steroids have been found to treat angiogenesis in a warm blooded mammal.

Derwent abstract 89-300681/41 discloses that suramin has anticancer utility.

SUMMARY OF INVENTION

Disclosed is a method of treating angiogenesis in a warm blooded mammal who is in need of such treatment which comprises administration of an angiogenic inhibiting amount of a combination of a suramin-type compound and an angiostatic steroid.

Also disclosed is a $\Delta^9(11)$ -etianic ester of formula (IV) where (A-I) R_{10} is α - $R_{10-1}:\beta$ - R_{10-2} where R_{10-2} is $-CH_3$, R_{10-1} and R_5 taken together are $-CH_2-CH_2-CR_2-CR_3-CH=$ where R_2 is α - $R_{2-1}:\beta$ - R_{2-2} where one of R_{2-1} and R_{2-2} is $-H$ and the other of R_{2-1} and R_{2-2} is $-H$, $-CH_3$, $-Cl$ or $-F$, where R_3 is $-O$ or α - $R_{3-1}:\beta$ - R_{3-2}

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where one R_{3-1} and R_{3-2} is -H and the other of R_{3-1} and R_{3-2} is - OR_{3-3} where R_{3-3} is -H, - $PO(OH)_2$ or - SO_3H ;

(A-II) R_{10} is α - $R_{10-3}:\beta$ - R_{10-4} where R_{10-4} is - CH_3 , R_{10-3} and R_5 taken together are - $CH-CH-CO-CH-$;

5 (A-III) R_{10} is α - $R_{10-5}:\beta$ - R_{10-6} and R_5 is α - $R_{5-5}:\beta$ - R_{5-6} , where R_{10-6} is - CH_3 , one of R_{5-5} and R_{5-6} is -H and the other of R_{5-5} and R_{5-6} taken with R_{10-5} is - $CH_2-CR_2-CR_3-CH_2-$ where R_2 and R_3 are as defined above;

10 R_6 is α - $R_{6-1}:\beta$ - R_{6-2} where one of R_{6-1} and R_{6-2} is -H and the other of R_{6-1} and R_{6-2} is -H, -F, -Cl, -Br and - CH_3 ;

R_7 is α - $R_{7-1}:\beta$ - R_{7-2} where one of R_{7-1} and R_{7-2} is -H and the other of R_{7-1} and R_{7-2} is -H or - CH_3 ;

R_{16} is - CH_2 or α - $R_{16-1}:\beta$ - R_{16-2} where one of R_{16-1} and R_{16-2} is -H and the other of R_{16-1} and R_{16-2} is -H, - CH_3 , -OH or -F;

15 R_{17} is C_1-C_{20} alkyl, C_1-C_{10} fluoroalkyl containing from 1-23 -F atoms, C_1-C_6 alkoxy, (C_1-C_8)alkylamino(C_1-C_6)alkyl, (C_5-C_7)cyclo-alkyl(C_1-C_6)alkyl, phenyl(C_1-C_6)alkyl optionally substituted with 1-3 - CH_3 , -F, -Cl, -OH, - OCH_3 , - OC_2H_5 and - NH_2 , C_3-C_8 cycloalkyl, C_2-C_{10} alkenyl, (C_3-C_8)cycloalkyl(C_2-C_{10}) alkenyl;

20 X is - $O-$ or - $S-$;

R_{21} is C_1-C_{10} alkyl optionally substituted with 1 to 10 -F, -Cl or -Br,

C_2-C_{10} alkyl substituted with 1 to 10 -OH,

25 - CH_2-COOR_{21-1} where R_{21-1} is C_1-C_{10} alkyl, C_3-C_8 cyclo-alkyl, C_3-C_8 cycloalkenyl, C_2-C_{10} alkenyl containing 1 thru 4 double bonds optionally substituted with -OH, -F, -Cl or -Br,

- $(CH_2)_{n1}$ -phenyl where n_1 is 0 or 1 and phenyl is optionally substituted with 1 thru 3 -F, -Cl, -Br, -OH, - OCH_3 , - OC_2H_5 , C_1-C_4 alkyl, - NH_2 , - $N(CH_3)_2$, - $N(C_2H_5)_2$ or - NO_2 ,

30 - $CH_2-CO-NR_{21-2}R_{21-3}$ where R_{21-2} and R_{21-3} are the same or different and are -H, C_1-C_{10} alkyl, C_3-C_8 cycloalkyl, - ϕ , - $CH_2-\phi$ and where R_{21-2} and R_{21-3} are taken together with the attached nitrogen atom to form a heterocyclic ring selected from the group consisting of 1-pyrrolidine, 1-piperidine, 1-piperazine and 1-morpholine.

DETAILED DESCRIPTION OF THE INVENTION

35 The present invention involves a method of treating angiogenesis in a warm blooded mammal which is in need of such treatment which

comprises administration of an angiogenic inhibiting amount of a combination of a suramin-type compound and an angiostatic steroid.

It is preferred that the mammal be a human.

Suramin-type compounds are compounds which mimic the anti-angiogenic action of suramin and which augment the activity of angiostatic steroids. Suramin and the suramin-type compounds are known to those skilled in the art. It is preferred that the suramin-type compound be selected from the group consisting of

- suramin,
- 10 3-hydroxy-2,7-naphthalenesulfonic acid,
- 4,5-dihydroxy-2,7-naphthalenedisulfonic acid,
- 2,2'-[(1,8-dihydroxy-3,6-disulfo-2,7-naphthylene)bis(azo)di-
- benzenearsonic acid,
- 15 4,4'-bis[[4-(o-hydroxyanilino)-6-(m-sulfoanilino)-s-triazin-2-yl]amino]-2,2'stilbenedisulfonic acid,
- 4,5-dihydroxy-3-[(p-nitrophenyl)azo]-2,7-naphthalenedisulfonic acid,
- 4,5-dihydroxy-3,6-bis[(4-sulfo-1-naphthyl)azo]-2,7-naphthalene-
- disulfonic acid,
- 20 3-[(5-chloro-2-hydroxyphenyl)azo]-4,5-dihydroxy-2,7-naphthalene-
- disulfonic acid,
- 4,5'-dihydroxy-3,6'[(3,3'-dimethoxy-4,4'-biphenyl)lene]bis(azo)-
- di-1-naphthalenesulfonic acid,
- 3,6-[(2,3-dimethyl-5-oxo-1-phenyl-3-pyrazolin-4-yl)azo]-4,5-
- 25 dihydroxy-2,7-naphthalenedisulfonic acid,
- 5,5'-[ureylenebis[2-sulfo-p-phenylene]azo]bis[6-amino-4-hydroxy-
- 2-naphthalenesulfonic acid,
- 4-[(o-arsenophenyl)azo]3-hydroxy-2,7-naphthalenedisulfonic acid,
- 4,5-dihydroxy-3-(phenylazo)-2,7-naphthalenedisulfonic acid,
- 30 4-acetamido-5-hydroxy-6-(phenylazo)-1,7-naphthalenedisulfonic acid,
- 2-[p-[(1-hydroxy-4-sulfo-2-naphthyl)azo]phenyl]-6-methyl-7-
- benzothiazolesulfonic acid,
- 4-[(2,4-dimethylphenyl)azo]-3-hydroxy-2,7-naphthalenedisulfonic
- 35 acid,
- 3-[(4-Sulfophenyl)azo]-4,5-dihydroxy-2,7-naphthalenedisulfonic acid,

3-[(4-nitr ph nyl)azo]-4-amino-5-hydroxy-2,7-naphthalene-disulfonic acid,

1-nitro-4,6,8-naphthalenetrisulfonic acid,

1-amino-4,6,8-naphthalenetrisulfonic acid and pharmaceutically acceptable salts thereof. It is more preferred that the suramin-type compound be suramin and 4,4'-bis[[4-(o-hydroxyanilino)-6-(m-sulfoanilino)-s-triazin-2-yl]amino]-2,2'stillbenedisulfonic acid. It is even more preferred that the suramin-type compound be suramin.

Angiostatic steroids refer to those steroids which prevent the process of angiogenesis/neovascularization, or cause the regression of new vasculature which results from angiogenic stimuli. Angiostatic steroids refer to, and include, the known 20-substituted steroids of formula (I) see US Patent 4,599,331, the known 21-hydroxy steroids of formula (II) see US Patent 4,771,042, the known C₁₁-functionalized steroids of formula (III) see International Patent Publication W087/02672, the following known steroids 6 α -fluoro-17 α ,21-dihydroxy-16 α -methylpregna-4,9(11)-diene-3,20-dione 21-acetate, 6 α -fluoro-17 α ,21-dihydroxy-16 β -methylpregna-4,9(11)-diene-3,20-dione, 6 α -fluoro-17 α ,21-dihydroxy-16 β -methylpregna-4,9(11)-diene-3,20-dione 21-phosphonoxy and pharmaceutically acceptable salts thereof, hydrocortisone, tetrahydrocortisol, 17 α -hydroxy-progesterone, 11 α -epihydrocortisone, cortexolone, corticosterone, desoxycorticosterone, dexamethasone, cortisone 21-acetate, hydrocortisone 21-phosphate, 17 α -hydroxy-6 α -methylpregn-4-ene-3,20-dione 17-acetate, 6 α -fluoro-17 α ,21-dihydroxy-16 α -methylpregna-4,9(11)-diene-3,20-dione and the novel Δ ⁹⁽¹¹⁾-etianic esters (IV).

The Δ ⁹⁽¹¹⁾-etianic esters (IV) are prepared by methods known to those skilled in the art from steroid starting material known to those skilled in the art, see CHART B. The starting materials for preparation of the Δ ⁹⁽¹¹⁾-etianic esters (IV) are the corresponding 17 α ,21-dihydroxy steroids (V). These compounds are oxidized by known procedures to remove C₂₁ and produce a steroid where C₂₀ is substituted with -X-H where X is -O- or -S-, rather than -CH₂-OH. The oxidation reaction is performed with an aqueous solution of an oxidizing agent such as periodate. It is preferred to use an excess of the oxidizing agent (about 2 equivalents). After refluxing the mixture for 1-10 hr the carboxylic acid product (VI) is isolated and

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can be purified by recrystallization as is known to those skilled in the art. The carb xylic acids (VI) are esterified at C₁₇ by reaction with the an anhydride of the desired corresponding 17-esters (VII). The anhydride is of the formula R₁₇-CO-O-CO-R₁₇ as is known to those skilled in the art, see US Patent 4,599,331. The 17-esters (VII) are then transformed to the desired $\Delta^{9(11)}$ -etianic esters (IV) by esterification procedures (for example with diazoalkyl reagents) well known to those skilled in the art.

With the $\Delta^{9(11)}$ -etianic esters (IV) it is preferred that R₃ is -O and it is further preferred that the steroid A-ring be Δ^4 -3-keto. It is preferred that R₆ is α -R₆₋₁: β -R₆₋₂ where R₆₋₂ is -H and R₆₋₁ is -H, -F and -CH₃, it is more preferred that R₆ is -F. It is preferred that R₇ is -H:-H. It is preferred that R₁₆ is α -R₁₆₋₁: β -R₁₆₋₂ where one of R₁₆₋₁ and R₁₆₋₂ is -H and the other of R₁₆₋₁ and R₁₆₋₂ is -CH₃. It is preferred that R₁₇ is C₁-C₄ alkyl or -(CF₂)_{n2}-CF₃ where n₂ is 0-3; it is more preferred that R₁₇ is -CH₃, -C₂H₅, -C₃H₇, -CF₃ or -CF₂-CF₃. It is preferred that R₂₁ is C₁-C₄ alkyl; it is more preferred that R₂₁ is -CH₃, -C₂H₅ or -C-(CH₃)₃. It is preferred that X is -O-.

It is preferred that the angiostatic steroid be $\Delta^{9(11)}$ -etianic esters of formula (IV) where

R₁₀ is α -R₁₀₋₁: β -R₁₀₋₂ where R₁₀₋₂ is -CH₃, R₁₀₋₁ and R₅ taken together are -CH₂-CR₂-CR₃-CH= where R₂ is -H:-H and R₃ is -O, R₆ is α -R₆₋₁: β -R₆₋₂ where R₆₋₂ is -H and R₆₋₁ is -H, -F and -CH₃,

R₇ is -H:-H,

R₁₆ is α -R₁₆₋₁: β -R₁₆₋₂ where one of R₁₆₋₁ and R₁₆₋₂ is -H and the other of R₁₆₋₁ and R₁₆₋₂ is -CH₃,

R₁₇ is C₁-C₄ alkyl or -(CF₂)_{n2}-CF₃ where n₂ is 0-3,

R₂₁ is C₁-C₄ alkyl,

X is -O-;

20-substituted steroids of formula (I), where

R₄ is -H,

R₆ and R₉ are be the same or different and are -H, -F, -Cl,

R₁₁ is chosen from the group consisting of hydroxy and ket,

R₂₀ is chosen from the group consisting of methoxy and

thiomethyl, and

R₁₇ is chosen from the group consisting of alkyl groups having less than 6 carbon atoms;

5 6 α -fluoro-17 α ,21-dihydroxy-16 α -methylpregna-4,9(11)-diene-3,20-dione 21-acetate,

6 α -fluoro-17 α ,21-dihydroxy-16 β -methylpregna-4,9(11)-diene-3,20-dione,

10 6 α -fluoro-17 α ,21-dihydroxy-16 β -methylpregna-4,9(11)-diene-3,20-dione 21-phosphonoxy, hydrocortisone, tetrahydrocortisol, 17 α -hydroxyprogesterone, 11 α -epihydrocortisone, cortexolone, corticosterone, desoxycorticosterone, dexamethasone, cortisone 21-acetate, hydrocortisone 21-phosphate, 17 α -hydroxy-6 α -methylpregn-4-ene-3,20-dione 17-acetate, 6 α -fluoro-17 α ,21-dihydroxy-16 α -methylpregna-4,9(11)-diene-3,20-dione.

15 It is more preferred that the angiostatic steroid be 6 α -fluoro-17 α ,21-dihydroxy-16 α -methylpregna-4,9(11)-diene-3,20-dione 21-acetate,

6 α -fluoro-17 α ,21-dihydroxy-16 β -methylpregna-4,9(11)-diene-3,20-dione,

20 6 α -fluoro-17 α ,21-dihydroxy-16 β -methylpregna-4,9(11)-diene-3,20-dione 21-phosphonoxy, hydrocortisone, tetrahydrocortisol, 17 α -hydroxyprogesterone, 11 α -epihydrocortisone, cortexolone, corticosterone, desoxycorticosterone, dexamethasone, cortisone 21-acetate, hydrocortisone 21-phosphate, 17 α -hydroxy-6 α -methylpregn-4-ene-3,20-dione 17-acetate, 6 α -fluoro-17 α ,21-dihydroxy-16 α -methylpregna-4,9(11)-diene-3,20-dione.

25 It is preferred that the method of treating angiogenesis is the treating of diseases of neovascularization. It is preferred that neovascular diseases are selected from the group consisting of solid tumors, diabetes, arthritis, atherosclerosis, neovascularization of the eye, parasitic diseases, psoriasis, abnormal wound healing processes, hypertrophy following surgery, burns, injury, hair growth, ovulation and corpus luteum formation, implantation and embryo development in the uterus. It is more preferred that the neovascular disease is solid tumors, diabetes, arthritis or psoriasis.

30 The suramin-type compounds and angiostatic steroids do not have to be administered in the same pharmaceutical dosage form. The

suramin-type compounds are usually administered IV b cause of their irritation wh r as the angiostatic ster ids can be administered either orally or parenterally (IM, SQ, IV).

5 The dose of the suramin-type compounds is from about 1 to about 1,000 mg/m²/day, preferably from about 5 to about 500 mg/m²/day. The suramin-type compound is given until the appropriate blood level is reached which is about 50 to about 300 µg/ml, preferably about 250 to about 300 µg/ml. At that point the administration of the suramin-type compound is stopped as is known to those skilled in the art.

10 10 The dose of the angiostatic steroids is from about 0.1 to about 100 mg/kg/day, preferably from about 0.1 to about 50 mg/kg/day.

15 For the inhibition of angiogenesis, angiostatic steroids may be combined with agents other than suramin including sulfated glycosaminoglycans and sulfated polysaccharides, or effective fragments of these molecules. The preferred glycosaminoglycans include heparin and heparan sulfate. Fragments of heparin or heparan sulfate may also be used if they contain a minimum of six saccharide residues; fragments of heparin or heparan sulfate may be prepared from heparin or heparan sulfate isolated from natural sources, or they may be 20 prepared by chemical synthesis. Angiostatic steroids may also be combined with polysaccharides including pentosan polysulphate, cyclodextrins, or other sulfated polysaccharides isolated from natural sources. The preferred polysaccharides are sulfated forms of β -cyclodextrin including β -cyclodextrin tetradecasulfate, pentosan 25 polysulphate, or the polysaccharide-peptidoglycan isolated from Arthrobacter, Journal of Biochemistry 92, 1775 (1982). These polysaccharides may be isolated from natural sources, or prepared by chemical synthesis.

30 Angiostatic steroids may also be used in combination treatments containing compounds which interfere with collagen biosynthesis. Preferred compounds in this group include L-azetidine-2-carboxylic acid, thioproline, and related proline analogs. Also included are other inhibitors of basement membrane collagen synthesis such as 8,9-dihydroxy-7-methyl-benzo(b)quinolizinium bromide.

35 The exact route of administration, dose, frequency of administration of both the suramin-type compound and angiostatic ster ids depends on the particular treatment of angiogenesis per-

formed, the severity of the disease, the age, general physical condition, weight, or other clinical abnormalities, etc., of the particular patient to be treated as is known to those skilled in the art.

5

DEFINITIONS AND CONVENTIONS

The definitions and explanations below are for the terms as used throughout this entire document including both the specification and the claims.

10

I. CONVENTIONS FOR FORMULAS AND DEFINITIONS OF VARIABLES

15

The chemical formulas representing various compounds or molecular fragments in the specification and claims may contain variable substituents in addition to expressly defined structural features. These variable substituents are identified by a letter or a letter followed by a numerical or letter subscript, for example, "Z₁" or "R_i" where "i" is an integer. These variable substituents are either monovalent or bivalent, that is, they represent a group attached to the formula by one or two chemical bonds. For example, a group Z₁ would represent a bivalent variable if attached to the formula CH₃-C(-Z₁)H. Groups R_i and R_j would represent monovalent variable substituents if attached to the formula CH₃-CH₂-C(R_i)(R_j)H₂. When chemical formulas are drawn in a linear fashion, such as those above, variable substituents contained in parentheses are bonded to the atom immediately to the left of the variable substituent enclosed in parentheses. When two or more consecutive variable substituents are enclosed in parentheses, each of the consecutive variable substituents is bonded to the immediately preceding atom to the left which is not enclosed in parentheses. Thus, in the formula above, both R_i and R_j are bonded to the preceding carbon atom. Also, for any molecule with an established system of carbon atom numbering, such as steroids, these carbon atoms are designated as C_i, where "i" is the integer corresponding to the carbon atom number. For example, C₆ represents the 6 position or carbon atom number in the steroid nucleus as traditionally designated by those skilled in the art of steroid chemistry. Likewise the term "R₆" represents a variable substituent (either monovalent or bivalent) at the C₆ position.

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Chemical formulas or portions thereof drawn in a linear fashion represent atoms in a linear chain. The symbol "-" in general repre-

sents a bond between two atoms in the chain. Thus $\text{CH}_3-\text{O}-\text{CH}_2-\text{CH}(\text{R}_1)-\text{CH}_3$ represents a 2-substituted-1-methoxypropane compound. In a similar fashion, the symbol "=" represents a double bond, e.g., $\text{CH}_2=\text{C}(\text{R}_1)-\text{O}-\text{CH}_3$, and the symbol "≡" represents a triple bond, e.g., 5 $\text{HC}\equiv\text{C}-\text{CH}(\text{R}_1)-\text{CH}_2-\text{CH}_3$. Carbonyl groups are represented in either one of two ways: $-\text{CO}-$ or $-\text{C}(-\text{O})-$, with the former being preferred for simplicity.

Chemical formulas of cyclic (ring) compounds or molecular fragments can be represented in a linear fashion. Thus, the compound 4-chloro-2-methylpyridine can be represented in linear fashion by 10 $\text{N}^*-\text{C}(\text{CH}_3)-\text{CH}=\text{CCl}-\text{CH}=\text{C}^*\text{H}$ with the convention that the atoms marked with an asterisk (*) are bonded to each other resulting in the formation of a ring. Likewise, the cyclic molecular fragment, 4-(ethyl)-1-piperazinyl can be represented by $-\text{N}^*-(\text{CH}_2)_2-\text{N}(\text{C}_2\text{H}_5)-\text{CH}_2-\text{C}^*\text{H}_2$. 15

When a variable substituent is bivalent, the valences may be taken together or separately or both in the definition of the variable. For example, a variable R_1 attached to a carbon atom as 20 $-\text{C}(-\text{R}_1)-$ might be bivalent and be defined as oxo or keto (thus forming a carbonyl group $(-\text{CO}-)$ or as two separately attached monovalent variable substituents $\alpha\text{-R}_{1-j}$ and $\beta\text{-R}_{1-k}$. When a bivalent variable, R_1 , is defined to consist of two monovalent variable substituents, the convention used to define the bivalent variable is 25 of the form " $\alpha\text{-R}_{1-j}:\beta\text{-R}_{1-k}$ " or some variant thereof. In such a case both $\alpha\text{-R}_{1-j}$ and $\beta\text{-R}_{1-k}$ are attached to the carbon atom to give $-\text{C}(\alpha\text{-R}_{1-j})(\beta\text{-R}_{1-k})-$. For example, when the bivalent variable R_6 , $-\text{C}(-\text{R}_6)-$ is defined to consist of two monovalent variable substituents, the 30 two monovalent variable substituents are $\alpha\text{-R}_{6-1}:\beta\text{-R}_{6-2}$, ..., $\alpha\text{-R}_{6-9}:\beta\text{-R}_{6-10}$, etc., giving $-\text{C}(\alpha\text{-R}_{6-1})(\beta\text{-R}_{6-2})-$, ..., $-\text{C}(\alpha\text{-R}_{6-9})(\beta\text{-R}_{6-10})-$, etc. Likewise, for the bivalent variable R_{11} , $-\text{C}(-\text{R}_{11})-$, two monovalent variable substituents are $\alpha\text{-R}_{11-1}:\beta\text{-R}_{11-2}$. For a ring substituent for which separate α and β orientations do not exist (e.g., due to the presence of a carbon carbon double bond in the ring), and for a substituent bonded to a carbon atom which is not 35 part of a ring the above convention is still used, but the α and β designations are omitted.

Just as a bivalent variable may be defined as two separate

monovalent variable substituents, two separate monovalent variable substituents may be defined to be taken together to form a bivalent variable. For example, in the formula $-C_1(R_i)H-C_2(R_j)H-$ (C_1 and C_2 define arbitrarily a first and second carbon atom, respectively) R_i and R_j may be defined to be taken together to form (1) a second bond between C_1 and C_2 or (2) a bivalent group such as oxa (-O-) and the formula thereby describes an epoxide. When R_i and R_j are taken together to form a more complex entity, such as the group $-X-Y-$, then the orientation of the entity is such that C_1 in the above formula is bonded to X and C_2 is bonded to Y . Thus, by convention the designation "... R_i and R_j are taken together to form $-CH_2-CH_2-O-CO-$..." means a lactone in which the carbonyl is bonded to C_2 . However, when designated "... R_j and R_i are taken together to form $-CO-O-CH_2-CH_2-$ the convention means a lactone in which the carbonyl is bonded to C_1 .

The carbon atom content of variable substituents is indicated in one of two ways. The first method uses a prefix to the entire name of the variable such as " C_1-C_4 ", where both "1" and "4" are integers representing the minimum and maximum number of carbon atoms in the variable. The prefix is separated from the variable by a space. For example, " C_1-C_4 alkyl" represents alkyl of 1 through 4 carbon atoms, (including isomeric forms thereof unless an express indication to the contrary is given). Whenever this single prefix is given, the prefix indicates the entire carbon atom content of the variable being defined. Thus C_2-C_4 alkoxy carbonyl describes a group $CH_3-(CH_2)_n-O-CO-$ where n is zero, one or two. By the second method the carbon atom content of only each portion of the definition is indicated separately by enclosing the " C_i-C_j " designation in parentheses and placing it immediately (no intervening space) before the portion of the definition being defined. By this optional convention $(C_1-C_3)-alkoxy carbonyl$ has the same meaning as C_2-C_4 alkoxy carbonyl because the " C_1-C_3 " refers only to the carbon atom content of the alkoxy group. Similarly, while both C_2-C_6 alkoxy alkyl and $(C_1-C_3)alkoxy(C_1-C_3)alkyl$ define alkoxy alkyl groups containing from 2 to 6 carbon atoms, the two definitions differ since the former definition allows either the alkoxy or alkyl portion alone to contain 4 or 5 carbon atoms while the latter definition limits either of these groups to 3 carbon atoms.

When the claims contain a fairly complex (cyclic) substituent, at the end of the phrase naming/designating that particular substituent will be a notation in (parentheses) which will correspond to the same name/designation in one of the CHARTS which will also set forth 5 the chemical structural formula of that particular substituent.

II. DEFINITIONS

All temperatures are in degrees Centigrade.

TLC refers to thin-layer chromatography.

THF refers to tetrahydrofuran.

10 ϕ refers to phenyl (C_6H_5).

MS refers to mass spectrometry expressed as m/e or mass/charge unit. $[M + H]^+$ refers to the positive ion of a parent plus a hydrogen atom. EI refers to electron impact. CI refers to chemical ionization. FAB refers to fast atom bombardment.

15 Ether refers to diethyl ether.

Pharmaceutically acceptable refers to those properties and/or substances which are acceptable to the patient from a pharmacological/toxicological point of view and to the manufacturing pharmaceutical chemist from a physical/chemical point of view regarding composition, formulation, stability, patient acceptance and bioavailability.

Treating refers to inhibiting and/or preventing.

Angiostatic steroids refer to those steroids which prevent the process of angiogenesis/neovascularization, or cause the regression 25 of new vasculature which results from angiogenic stimuli.

When solvent pairs are used, the ratios of solvents used are volume/volume (v/v).

EXAMPLES

Without further elaboration, it is believed that one skilled in 30 the art can, using the preceding description, practice the present invention to its fullest extent. The following detailed examples describe how to prepare the various compounds and/or perform the various processes of the invention and are to be construed as merely illustrative, and not limitations of the preceding disclosure in any way whatsoever. Those skilled in the art will promptly recognize appropriate variations from the procedures both as to reactants and 35 as to reaction conditions and techniques.

PREPARATION 1 6α -Fluoro- $17\alpha,21$ -dihydroxy- 16α -methylpregna-4,9(11)-diene-3,20-dione (V)

Methanol (20 ml) and sodium methoxide (25%, 0.2 ml) is added to 6α -fluoro- $17\alpha,21$ -dihydroxy- 16α -methylpregna-4,9(11)-diene-3,20-dione 21-acetate (US Patent 3,291,815, 1.0 g) in methanol. The reaction mixture is neutralized with acetic acid and concentrated to dryness under reduced pressure. The concentrate is distributed between water and chloroform. The organic layer is separated and washed twice with water and dried over anhydrous sodium sulfate. The crude solid is chromatographed over silica gel eluting with ethyl acetate/hexane (35/65). The appropriate fractions are pooled and concentrated to give the title compound, mp 206-207°.

PREPARATION 2 6α -Fluoro- $17\alpha,21$ -dihydroxy- 16α -methylpregna-1,4,9(11)-triene-3,20-dione (V)

Following the general procedure of PREPARATION 1 and making non-critical variations but starting with 6α -fluoro- $17\alpha,21$ -dihydroxy- 16α -methylpregna-4,9(11)-diene-3,20-dione 21-acetate (US Patent 4,704,358), the title compound is obtained.

EXAMPLE 1 6α -Fluoro- 17α -hydroxy- 16α -methylandrosta-4,9(11)-dien-3-one 17β -carboxylic acid (VI)

THF (26 ml) and periodic acid (0.677 g) in water (10 ml) is added to 611 mg (1.62 mmol) of 6α -fluoro- $17,21$ -dihydroxy- 16α -methylpregna-4,9(11)-diene-3,20-dione (V, PREPARATION 1, 611 mg). The resulting solution is heated at reflux for 2 hours, then cooled to 25° and concentrated under reduced pressure to a volume of 5 ml. Water (15 ml) is added to the residue and the resulting mixture is extracted with ethyl acetate (2 x 25 ml). The ethyl acetate extracts are combined, dried over anhydrous sodium sulfate, filtered, and concentrated to dryness. The crude material is crystallized from acetone/hexane to give the title compound, mp 213.8-214°, MS calculated 363.1971, found 363.1962.

EXAMPLE 2 6α -Fluoro- 17α -hydroxy- 16α -methylandrosta-4,9(11)-dien-3-one 17β -carboxylic acid methyl ester 17-acetate (IV)

35

Part I

Acetic anhydride (0.5 ml) and triethylamine (0.3 ml) are added to 6α -fluoro- 17α -hydroxy- 16α -methylandrosta-4,9(11)-dien-3-one 17β -

carboxylic acid (VI, EXAMPLE 1, 300 mg). The resulting mixture is stirred at 20-25° until dissolution occurs, and then stirred for an additional 40 min. The reaction solution is concentrated to dryness under reduced pressure, and the residue is dissolved in methanol and 5 allowed to sit at 25° for 30 min. Evaporation of the methanol and final drying under high vacuum gives crude 6 α -fluoro-17 α -hydroxy-16 α -methylandrosta-4,9(11)-dien-3-one 17 β -carboxylic acid 17-acetate (VII) in quantitative yield, TLC R_f = 0.05 (ethyl acetate/hexane, 35/65).

10

Part 2

The crude 17-acetate (VII) is dissolved in THF (8 ml) and then treated with freshly prepared diazomethane in ether until all of the starting material appeared to have reacted by TLC. The crude product is purified by chromatography over silica gel eluting with ethyl 15 acetate/hexane (25/75). The appropriate fractions are pooled and concentrated to give the title compound, TLC R_f = 0.6 (ethyl acetate/hexane (35/65); MS calculated 419.2234, found 419.2212.

EXAMPLE 3 6 α -Fluoro-17 α -hydroxy-16 α -methylandrosta-4,9(11)-dien-3-one 17 β -carboxylic acid methyl ester 17-trifluoroacetate (IV)

20 Following the general procedure of EXAMPLE 2 (Parts I and II) and making non-critical variations but using trifluoroacetic anhydride, the title compound is obtained, MS calculated 473.1951, found 473.1944.

EXAMPLE 4 25 6 α -Fluoro-17 α -hydroxy-16 α -methylandrosta-4,9(11)-dien-3-one 17 β -carboxylic acid methyl ester 17-propionate (IV)

Following the general procedure of EXAMPLE 2 (Part I) and making 30 non-critical variations but using propionic anhydride, 6 α -fluoro-17 α -hydroxy-16 α -methylandrosta-4,9(11)-dien-3-one 17 β -carboxylic acid 17-propionate (VII), is obtained, TLC R_f = 0.05 (ethyl acetate/hexane, 35/65); MS calculated 419.2234, found 419.2212.

Following the general procedure of EXAMPLE 2 (Part II) and 35 making non-critical variations but starting with 6 α -fluoro-17 α -hydroxy-16 α -methylandrosta-4,9(11)-dien-3-one 17 β -carboxylic acid 17-propionate (VII), the title compound is obtained, TLC R_f = 0.5 (ethyl acetate/hexane, 35/65); MS calculated 433.2390, found 433.2377.

EXAMPLE 5 6α -Fluoro- 17α -hydroxy- 16α -methylandrosta-4,9(11)-dien-3-one 17β -carboxylic acid methyl ester 17-pentafluoropropionate (IV)

Following the general procedure of EXAMPLE 2 (Parts I and II) but using pentafluoropropionic anhydride, the title compound is obtained, TLC R_f = 0.05 (ethyl acetate/hexane, 35/65); MS calculated 523.1919, found 523.1952.

EXAMPLE 6 6α -Fluoro- 17α -hydroxy- 16α -methylandrosta-4,9(11)-dien-3-one 17β -carboxylic acid methyl ester 17-butyrate (IV)

Following the general procedure of EXAMPLE 2 (Part I) and making non-critical variations but using butyric anhydride, 6α -fluoro- 17α -hydroxy- 16α -methylandrosta-4,9(11)-dien-3-one 17β -carboxylic acid 17-butyrate (VII), is obtained, TLC R_f = 0.05 (ethyl acetate/hexane, 35/65); MS calculated 433.2390, found 433.2377.

Following the general procedure of EXAMPLE 2 (Part II) and making non-critical variations but starting with 6α -fluoro- 17α -hydroxy- 16α -methylandrosta-4,9(11)-dien-3-one 17β -carboxylic acid 17-butyrate (VII), the title compound is obtained, TLC R_f = 0.5 (ethyl acetate/hexane, 35/65); MS calculated 447.2547, found 447.2533.

EXAMPLE 7 6α -Fluoro- 17α -hydroxy- 16β -methylandrosta-4,9(11)-dien-3-one 17β -carboxylic acid (VI)

Following the general procedure of EXAMPLE 1 and making non-critical variations but starting with 6α -fluoro-17,21-dihydroxy- 16β -methylpregna-4,9(11)-diene-3,20-dione (V, US Patent 4,088,537, Preparation 3, 3.00 g), the title compound is obtained, mp 215-216° with decomposition; MS calculated 363.1971, found 363.1952.

EXAMPLE 8 6α -Fluoro- 17α -hydroxy- 16β -methylandrosta-4,9(11)-dien-3-one 17β -carboxylic acid methyl ester

Following the general procedure of EXAMPLE 2 (Part II) but starting with 6α -fluoro- 17α -hydroxy- 16β -methylandrosta-4,9(11)-dien-3-one 17β -carboxylic acid (VI, EXAMPLE 7, 181 mg), the title compound is obtained, TLC R_f = 0.8 (ethyl acetate/chloroform, 25/75), mp 181-182°; MS calculated 377.2128, found 377.2146.

EXAMPLE 9 6α -Fluoro- 17α -hydroxy- 16β -methylandrosta-4,9(11)-dien-3-one 17β -carboxylic acid methyl ester 17-propionate (IV)

Following the general procedure of EXAMPLE 4 but starting with 6 α -fluoro-17 α -hydroxy-16 β -methylandrosta-4,9(11)-dien-3-one 17 β -carboxylic acid (VI, EXAMPLE 7, 250 mg), 6 α -fluoro-17 α -hydroxy-16 β -methylandrosta-4,9(11)-dien-3-one 17 β -carboxylic acid 17-propionate (VII), mp 191° with bubbling; MS calculated 419.2234, found 419.2250 and 6 α -fluoro-17 α -hydroxy-16 β -methylandrosta-4,9(11)-dien-3-one 17 β -carboxylic acid methyl ester 17-propionate (IV) are obtained, TLC R_f = 0.8 (ethyl acetate/hexane, 25/75); mp 165-166°; MS calculated 433.2390, found 433.2398.

EXAMPLE 10 6 α -Fluoro-17 α -hydroxy-16 β -methylandrosta-4,9(11)-dien-3-one 17 β -carboxylic acid methyl ester 17-butyratate (IV)

Following the general procedure of EXAMPLE 6 but starting with 6 α -fluoro-17 α -hydroxy-16 β -methylandrosta-4,9(11)-dien-3-one 17 β -carboxylic acid (VI, EXAMPLE 7), 6 α -fluoro-17 α -hydroxy-16 β -methylandrosta-4,9(11)-dien-3-one 17 β -carboxylic acid 17-butyratate (VII), mp 150-152°; MS calculated 433.2390, found 433.2418 and 6 α -fluoro-17 α -hydroxy-16 β -methylandrosta-4,9(11)-dien-3-one 17 β -carboxylic acid methyl ester 17-butyratate (IV) are obtained, TLC R_f = 0.8 (ethyl acetate/hexane, 25/75), mp 166-167°; MS calculated 447.2547, found 447.2564.

EXAMPLE 11 6 α -Fluoro-17 α -hydroxy-16 α -methylandrosta-1,4,9(11)-trien-3-one 17 β -carboxylic acid (VI)

Following the general procedure of EXAMPLE 1 and making non-critical variations but starting with 6 α -fluoro-17 α ,21-dihydroxy-16 α -methylpregna-1,4,9(11)-triene-3,20-dione (V, PREPARATION 2, 0.25 g), the title compound is obtained, mp 204.8-205.3°; MS calculated (for $C_{21}H_{25}FO_4$) 360.1737, found 360.1715.

EXAMPLE 12 6 α -Fluoro-17 α -hydroxy-16 α -methylandrosta-1,4,9(11)-trien-3-one 17 β -carboxylic acid methyl ester 17-propionate (IV)

Following the general procedure of EXAMPLE 2 (Parts I and II) and making non-critical variations but starting with 6 α -fluoro-17 α -hydroxy-16 α -methylandrosta-1,4,9(11)-trien-3-one 17 β -carboxylic acid (VI, EXAMPLE 11, 250 mg) and using propionic anhydride, the title compound is obtained, mp 172-172.5°; TLC R_f = 0.6 (ethyl acetate/hexane, 35/65), MS calculated (for $C_{25}H_{31}FO_5$) 430.2155, found

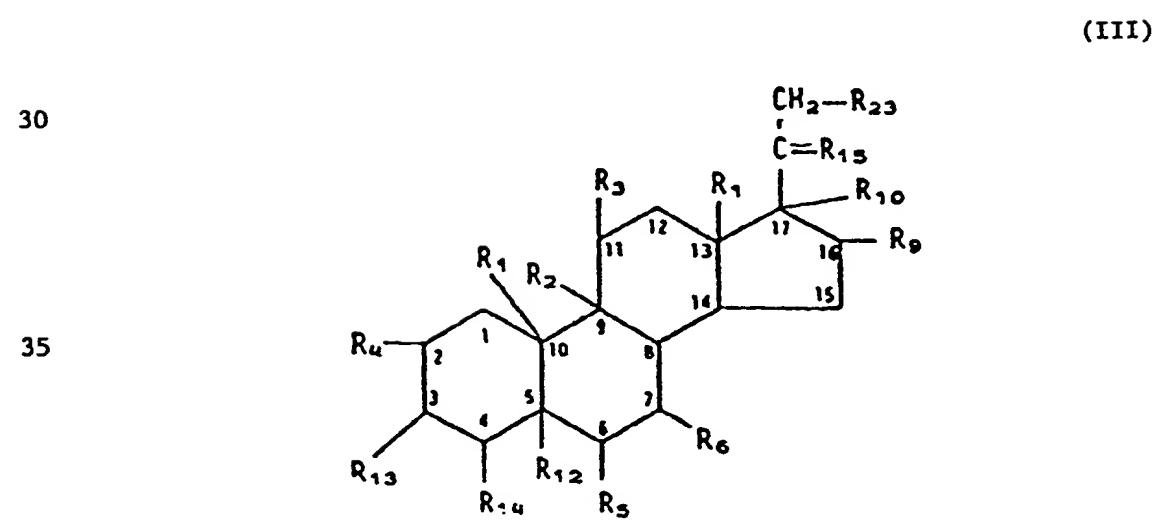
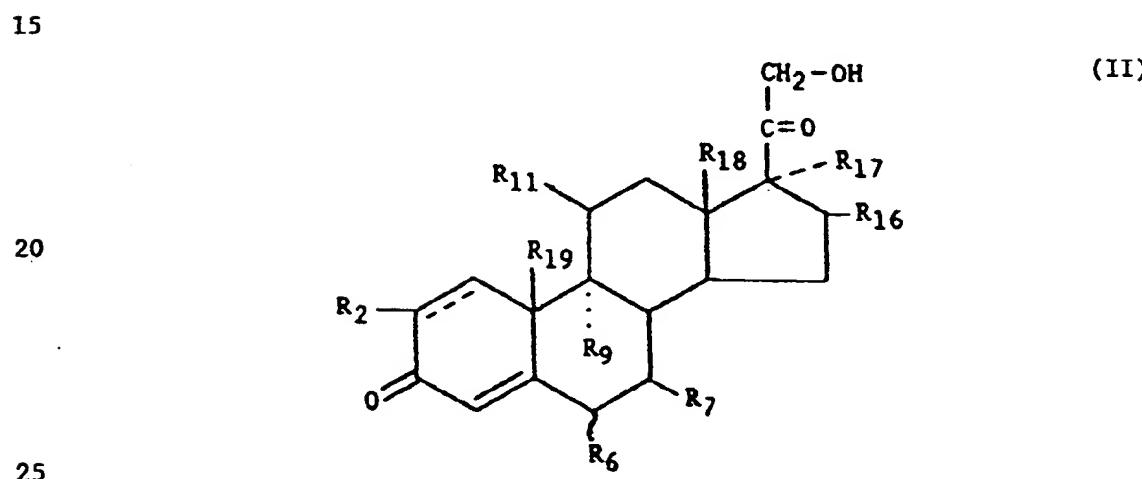
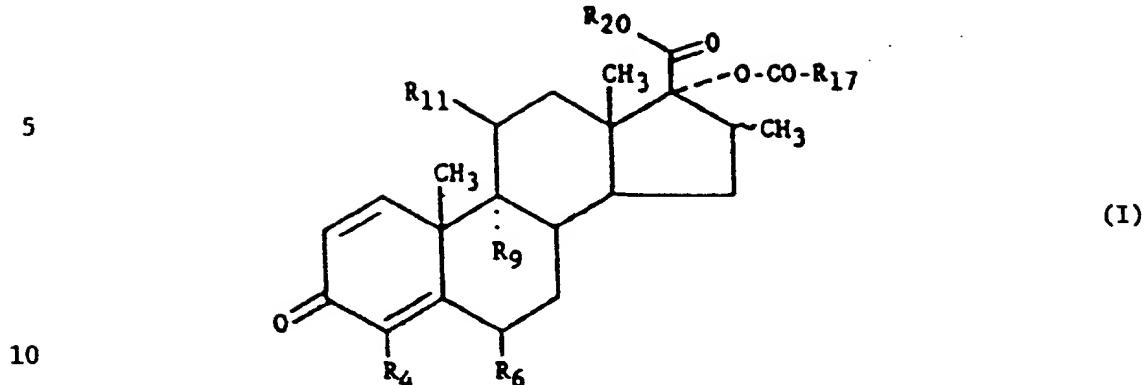
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430.2156.

EXAMPLE 13 6α -Fluoro- 17α -hydroxy- 16α -methylandrosta-1,4,9(11)-trien-3-one 17β -carboxylic acid methyl ester 17-butyrate (IV)

5 Following the general procedure of EXAMPLE 2 (Parts I and II) and making non-critical variations but starting with 6α -fluoro- 17α -hydroxy- 16α -methylandrosta-1,4,9(11)-trien-3-one 17β -carboxylic acid (VI, EXAMPLE 11, 250 mg) and using butyric anhydride, the title compound is obtained, TLC R_f = 0.6 (ethyl acetate/hexane, 35/65); mp 10 141-141.5°; MS calculated (for $C_{26}H_{33}FO_5$) 444.2312, found 444.2309.

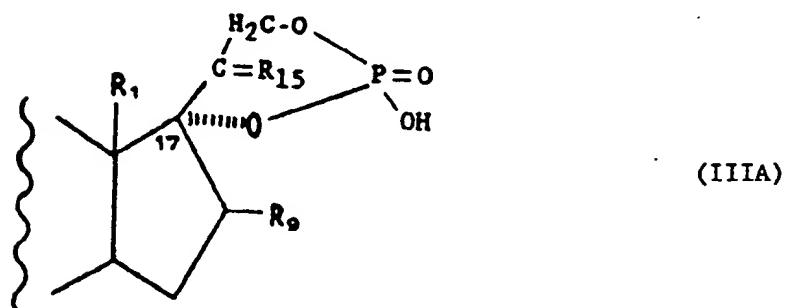
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CHART A

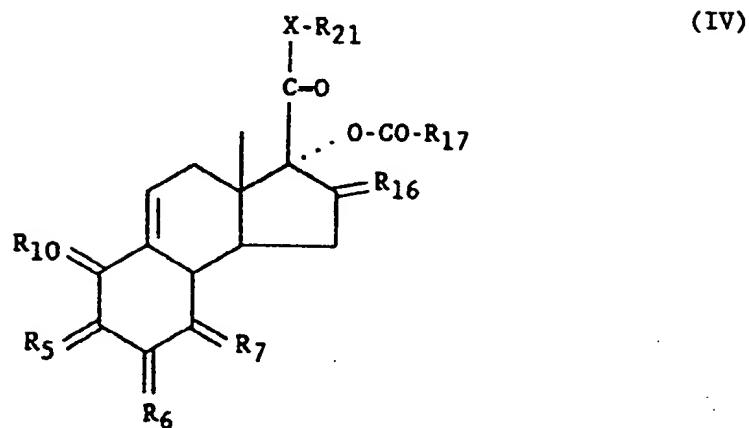
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CHART A - Continued

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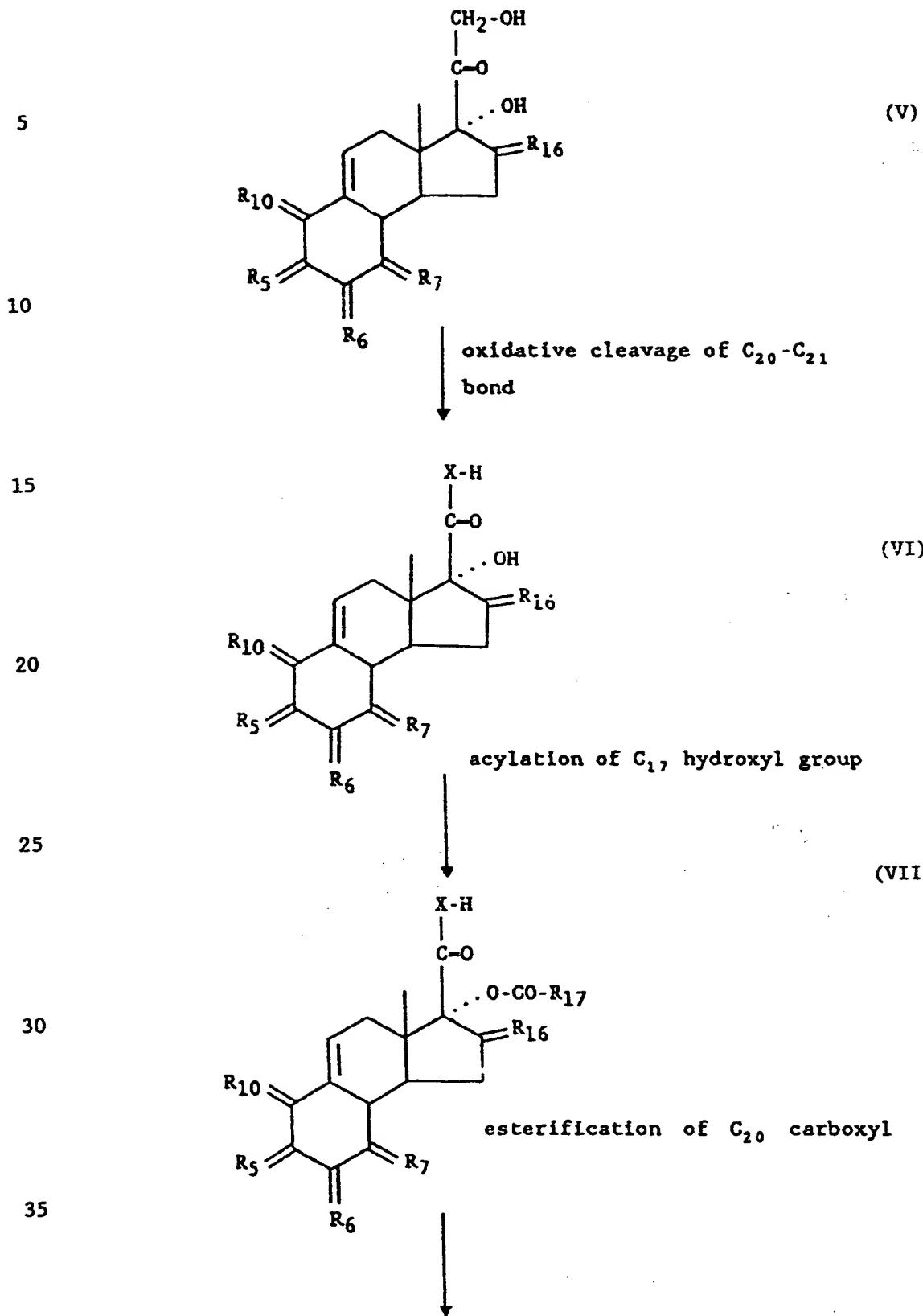


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CHART B



CLAIMS

1. A method of treating angiogenesis in a warm blooded mammal who is in need of such treatment which comprises administration of an angiogenic inhibiting amount of a combination of a suramin-type compound and an angiostatic steroid.
- 5
2. A method of treating angiogenesis according to claim 1 where the mammal is a human.
- 10 3. A method of treating angiogenesis according to claim 1 where the suramin-type compound is selected from the group consisting of suramin, 3-hydroxy-2,7-naphthalenesulfonic acid, 4,5-dihydroxy-2,7-naphthalenedisulfonic acid, 15 2,2'-[(1,8-dihydroxy-3,6-disulfo-2,7-naphthylene)bis(azo)dibenzene]arsonic acid, 4,4'-bis[[4-(o-hydroxyanilino)-6-(m-sulfoanilino)-s-triazin-2-yl]amino]-2,2'stilbenedisulfonic acid, 4,5-dihydroxy-3-[(p-nitrophenyl)azo]-2,7-naphthalenedisulfonic 20 acid, 4,5-dihydroxy-3,6-bis[(4-sulfo-1-naphthyl)azo]-2,7-naphthalenedisulfonic acid, 3-[(5-chloro-2-hydroxyphenyl)azo]-4,5-dihydroxy-2,7-naphthalenedisulfonic acid, 25 4,5'-dihydroxy-3,6'[(3,3'-dimethoxy-4,4'-biphenylylene)bis(azo)-di-1-naphthalenesulfonic acid, 3,6-[(2,3-dimethyl-5-oxo-1-phenyl-3-pyrazolin-4-yl)azo]-4,5-dihydroxy-2,7-naphthalenedisulfonic acid, 30 5,5'-[ureylenebis[2-sulfo-p-phenylene)azo]bis[6-amino-4-hydroxy-2-naphthalenesulfonic acid, 4-[(o-arsenophenyl)azo]3-hydroxy-2,7-naphthalenedisulfonic acid, 4,5-dihydroxy-3-(phenylazo)-2,7-naphthalenedisulfonic acid, 4-acetamido-5-hydroxy-6-(phenylazo)-1,7-naphthalenedisulfonic 35 acid, 2-[p-[(1-hydroxy-4-sulfo-2-naphthyl)azo]phenyl]-6-methyl-7-benzothiazolesulfonic acid, 4-[(2,4-dimethylphenyl)azo]-3-hydroxy-2,7-naphthalenedisulfonic

acid,

3-[(4-Sulfophenyl)azo]-4,5-dihydroxy-2,7-naphthalenedisulfonic acid,

5 3-[(4-nitrophenyl)azo]-4-amino-5-hydroxy-2,7-naphthalene-disulfonic acid,

1-nitro-4,6,8-naphthalenetrisulfonic acid,

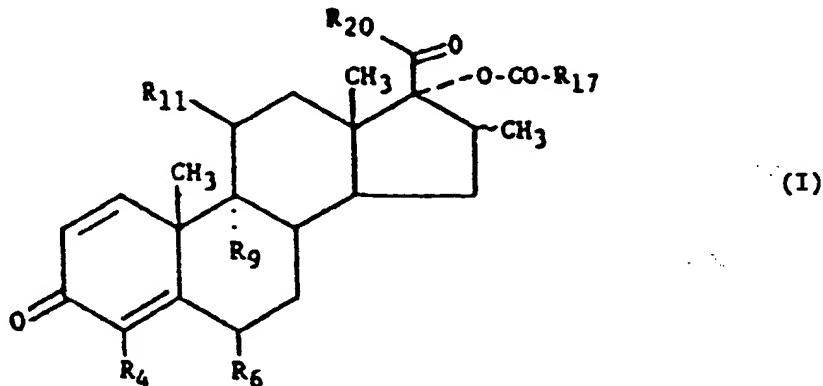
1-amino-4,6,8-naphthalenetrisulfonic acid and pharmaceutically acceptable salts thereof.

10 4. A method of treating angiogenesis according to claim 1 where the suramin-type compound is suramin and 4,4'-bis[[4-(o-hydroxyanilino)-6-(m-sulfoanilino)-s-triazin-2-yl]amino]-2,2'stilbenedisulfonic acid.

15 5. A method of treating angiogenesis according to claim 1 where the suramin-type compound is suramin.

6. A method of treating angiogenesis according to claim 1 where the angiostatic steroid is selected from the group consisting of
20-substituted steroids of formula (I)

20



25

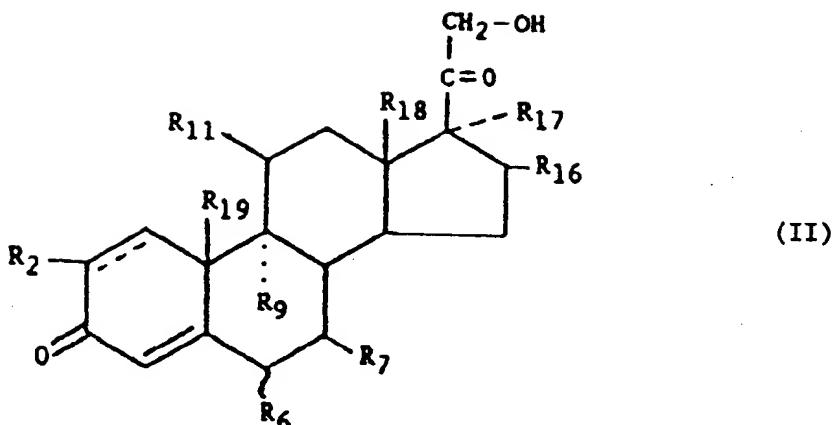
where

30 R₄, R₆ and R₉ are be the same or different and are -H, -F, -Cl;
R₁₁ is chosen from the group consisting of hydroxy and keto;
R₂₀ is chosen from the group consisting of hydroxy, methoxy and thiomethyl; and

35 R₁₇ is chosen from the group consisting of alkyl groups having less than 6 carbon atoms;

21-hydroxy steroids of formula (II)

-23-



10 where

the dotted line between positions C-1 and C-2 means the presence or absence of a double bond; the ~ bond at C-6 denotes α or β ;

R₁₈ is CH₃ or -C₂H₅;

R₁₉ is CH₃ or -C₂H₅;

15 R₉ is H, and R₁₁ is in the α -position and is -OH, -O-alkyl-(C₁-C₁₂), -OC(-O)alkyl(C₁-C₁₂), -OC(-O)aryl, -OC(-O)N(R)₂, or -OC(-O)OR₉₋₁, where aryl is furyl, thienyl, pyrrolyl, or pyridyl optionally substituted with one or two (C₁-C₄)-alkyl groups or aryl is -(CH₂)_f-phenyl wherein f is 0 to 2 and wherein the phenyl ring is

20 optionally substituted with one to three groups selected from chlorine, fluorine, bromine, alkyl(C₁-C₃), alkoxy(C₁-C₃), thioalkoxy-(C₁-C₃), Cl₃C-, F₃C-, -NH₂ and -NHCOCH₃ and wherein R is hydrogen, alkyl(C₁-C₄), or phenyl and each R can be the same or different; and

R₉₋₁ is aryl as herein defined or alkyl(C₁-C₁₂); or

25 R₉ is α -Cl and R₁₁ is β -Cl; or

R₉ and R₁₁ taken together are oxygen (-O-) bridging positions C-9 and C-11; or

30 R₉ and R₁₁ taken together form a double bond between positions C-9 and C-11;

R₂ is H, CH₃, Cl or F;

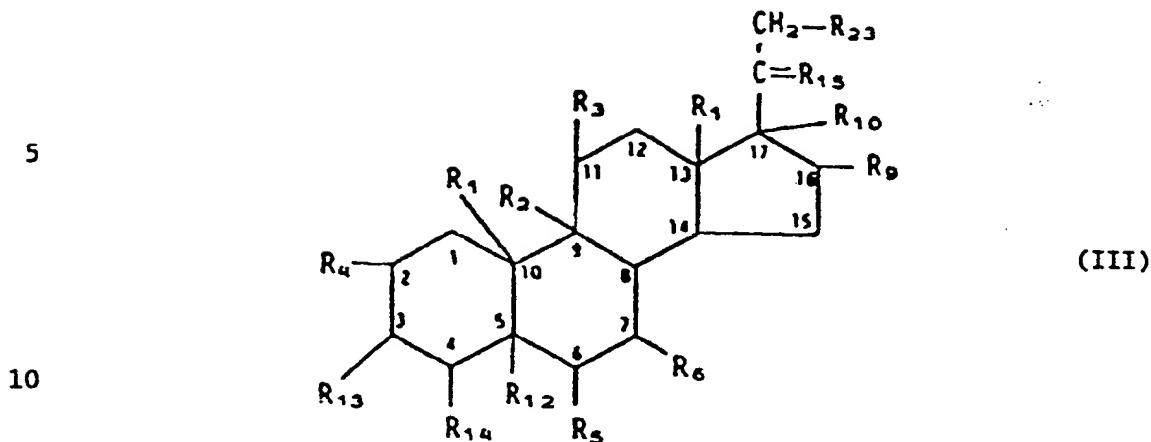
R₆ is H, OH, F, Cl, Br, CH₃, phenyl, vinyl or allyl;

R₇ is H or CH₃;

R₁₆ is -CH₂ or α -R₁₆₋₁: β -R₁₆₋₂ where one of R₁₆₋₁ and R₁₆₋₂ is -H and the other of R₁₆₋₁ and R₁₆₋₂ is H, OH, CH₃ or F; and

35 R₁₇ is H, OH, CH₃ or R₁₆ and R₁₇ are taken together to form a second bond between positions C-16 and C-17;

C₁₁-functionalized steroids of formula (III)



where

R₁ is β -CH₃ or β -CH₂H₅;

wherein R₂ is H, and R₃ is -O, OH, -O-alkyl(C₁-C₁₂), -OC(-O)-alkyl-(C₁-C₁₂), -OC(-O)aryl, -OC(-O)N(R)₂, or -OC(-O)OR₇, wherein aryl is furyl, thieryl, pyrrolyl, or pyridyl wherein each of said hetero moiety is optionally substituted with one or two (C₁-C₄)alkyl groups or aryl is -(CH₂)_f-phenyl wherein f is 0 to 2 and wherein the phenyl ring is optionally substituted with one to 3 groups selected from chlorine, bromine, alkyl(C₁-C₃), alkoxy(C₁-C₃), thioalkoxy(C₁-C₃), Cl₃C-, F₃C-, -NH₂ and -NHCOCH₃ and wherein R is hydrogen, alkyl(C₁-C₄), or phenyl and each R can be the same or different; and wherein R₇ is aryl as hereindefined or alkyl(C₁-C₁₂); or wherein R₂ is α -Cl and R₃ is β -Cl; or wherein R₂ and R₃ taken together are oxygen (-O-) bridging positions C-9 and C-11; wherein R₂ and R₃ taken together form a second bond between positions C-9 and C-11; or R₂ is α -F and R₃ is β -OH;

wherein R₄ is H, CH₃, Cl or F;

wherein R₅ is α -R₅₋₁: β -R₅₋₂ where one of R₅₋₁ and R₅₋₂ is -H and the other of R₅₋₁ and R₅₋₂ is H, OH, F, Cl, Br, CH₃, phenyl, vinyl or allyl;

wherein R₆ is H or CH₃;

wherein R₉ is -CH₂ or α -R_{9-1: β -R₉₋₂ where one of R₉₋₁ and R₉₋₂ is -H and the other is H, OH, CH₃, F or -CH₂;}

35 wherein R₁₀ is H, α -OH, α -CH₃ or R₁₀ forms a second bond between positions C-16 and C-17;

wherein R₁₂ is α -H, β -H or forms a second bond with R₁₄;

wherein R_{13} is $-O$ or α - $R_{13-1}:\beta$ - R_{13-2} where one of R_{13-1} and R_{13-2} is $-H$ and the other of R_{13-1} and R_{13-2} is $-OH$, $-O-P(O)(OH)_2$, or $-O-C(-O)-(CH_2)_tCOOH$ where t is an integer from 2 to 6;
 wherein R_{14} is H or forms a second bond with R_{12} ;

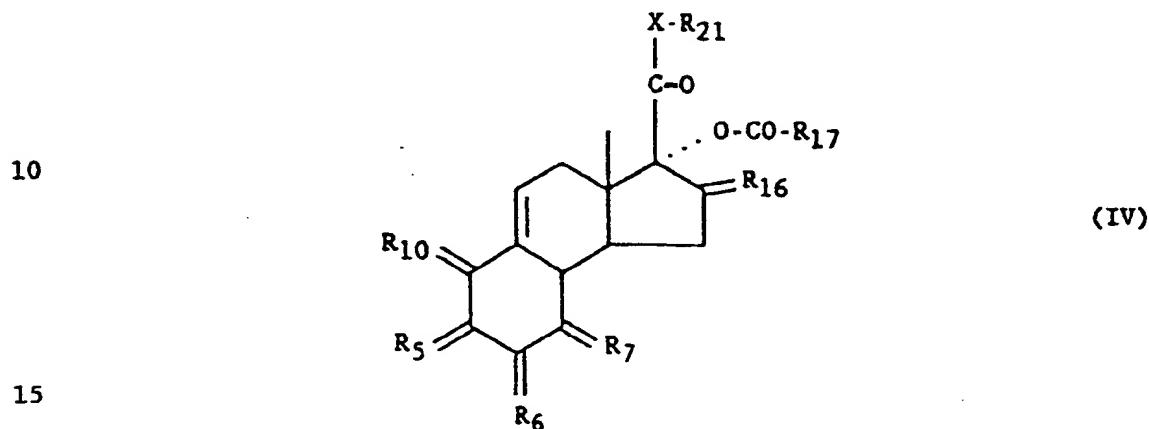
5 wherein R_{15} is $-O$ or α - $R_{15-1}:\beta$ - R_{15-2} where one of R_{15-1} and R_{15-2} is $-H$ and the other is $-OH$;
 wherein R_{23} with R_{10} forms a cyclic phosphate of the formula IV
 wherein R_9 and R_{15} have the meaning defined above; or wherein R_{23} is $-OH$, $O-C(-)-R_{11}$, $-O-P(O)(OH)_2$, or $-O-C(-O)-(CH_2)_tCOOH$ wherein t is an
 10 integer from 2 to 6; and R_{11} is $-Y-(CH_2)_n-X-(CH_2)_m-SO_3H$, $-Y'-(CH_2)_p-$
 $X'-(CH_2)_q-NR_{16}R_{17}$ or $-Z(CH_2)_rQ$, wherein Y is a bond or $-O-$; Y' is a
 bond, $-O-$, or $-S-$; each of X and X' is a bond, $-CON(R_{18})-$, $-N(R_{18})CO-$
 $-O-$, $-S-$, $-S(O)-$, or $-S(O_2)-$; R_{18} is hydrogen or alkyl(C_1-C_4); each
 15 of R_{16} and R_{17} is a lower alkyl group of from one to 4 carbon atoms
 optionally substituted with one hydroxyl or R_{16} and R_{17} taken
 together with the nitrogen atom to which each is attached forms a
 monocyclic heterocyclic selected from pyrrolidino, piperidino,
 morpholino, thiomorpholino, piperazino or N (lower)alkylpiperazino
 wherein alkyl has from one to 4 carbon atoms; n is an integer of from
 20 4 to 9; m is an integer of from one to 5; p is an integer of from 2
 to 9; q is an integer of from one to 5; Z is a bond or $-O-$; r is an
 integer of from 2 to 9; and Q is
 $(1) -R_{19}-CH_2COOH$ wherein R_{19} is $-S-$, $-S(O)-$, $-S(O)_2-$, $-SO_2N-$
 $(R_{20})-$, or $-N(R_{20})SO_2-$; and R_{20} is hydrogen or lower alkyl(C_1-C_4);
 25 with the proviso that the total number of carbon atoms in R_{20} and
 $(CH_2)_r$ is not greater than 10;
 $(2) -CO-COOH$; or
 $(3) -CON(R_{21})CH(R_{22})COOH$ wherein R_{21} is H and R_{22} is H , CH_3 ,
 $-CH_2COOH$, $-CH_2CH_2COOH$, $-CH_2OH$, $-CH_2SH$, $-CH_2CH_2SCH_3$, or $-CH_2Ph-OH$
 30 wherein $Ph-OH$ is p-hydroxyphenyl; or R_{21} is CH_3 and R_{22} is H ; or R_{21}
 and R_{22} taken together are $-CH_2CH_2CH_2-$; or $-N(R_{21})CH(R_{22})COOH$ taken
 together is $-NHCH_2CONHCH_2COOH$; and pharmaceutically acceptable salts
 thereof; with the further provisos that:
 (a) when n is 2, R_{18} is other than hydrogen;
 35 (b) the sum of m and n is not greater than 10;
 (c) the sum of p and q is not greater than 10;
 (d) when X is a bond the sum of m and n is from 5 to 10;

() when X' is a bond the sum of p and q is from 4 to 9;

(f) when R₄ is Cl or F, the C-1 position is saturated; and

(g) when R₉ is -CH₂, R₁₀ is other than a second bond between positions C-16 and C-17; and mono and bis salts thereof;

5 $\Delta^{9(11)}$ -etianic esters of formula (IV)



where

(A-I) R₁₀ is α -R₁₀₋₁: β -R₁₀₋₂ where R₁₀₋₂ is -CH₃,

R₁₀₋₁ and R₅ taken together are -CH₂-CR₂-CR₃-CH- where R₂ is

20 α -R₂₋₁: β -R₂₋₂ where one of R₂₋₁ and R₂₋₂ is -H and the other of R₂₋₁ and R₂₋₂ is -H, -CH₃, -Cl or -F, where R₃ is -O or α -R₃₋₁: β -R₃₋₂ where one R₃₋₁ and R₃₋₂ is -H and the other of R₃₋₁ and R₃₋₂ is -OR₃₋₃ where R₃₋₃ is -H, -PO(OH)₂ or -SO₃H;

(A-II) R₁₀ is α -R₁₀₋₃: β -R₁₀₋₄ where R₁₀₋₄ is -CH₃, R₁₀₋₃ and R₅ taken together are -CH=CH-CO-CH=;

(A-III) R₁₀ is α -R₁₀₋₅: β -R₁₀₋₆ and R₅ is α -R₅₋₅: β -R₅₋₆, where R₁₀₋₆ is -CH₃, one of R₅₋₅ and R₅₋₆ is -H and the other of R₅₋₅ and R₅₋₆ taken with R₁₀₋₅ is -CH₂-CR₂-CR₃-CH₂- where R₂ and R₃ are as defined above;

30 R₆ is α -R₆₋₁: β -R₆₋₂ where one of R₆₋₁ and R₆₋₂ is -H and the other of R₆₋₁ and R₆₋₂ is -H, -F, -Cl, -Br and -CH₃;

R₇ is α -R₇₋₁: β -R₇₋₂ where one of R₇₋₁ and R₇₋₂ is -H and the other of R₇₋₁ and R₇₋₂ is -H or -CH₃;

R₁₆ is -CH₂ or α -R₁₆₋₁: β -R₁₆₋₂ where one of R₁₆₋₁ and R₁₆₋₂ is -H and the other of R₁₆₋₁ and R₁₆₋₂ is -H, -CH₃, -OH or -F;

R₁₇ is C₁-C₂₀ alkyl, C₁-C₁₀ fluor alkyl containing from 1-23 -F atoms, C₁-C₆ alkoxy, (C₁-C₈)alkylamino(C₁-C₆)alkyl, (C₅-C₇)cycl -

alkyl(C₁-C₆)alkyl, phenyl(C₁-C₆)alkyl optionally substituted with 1-3 -CH₃, -F, -Cl, -OH, -OCH₃, -OC₂H₅ and -NH₂, C₃-C₈ cycloalkyl, C₂-C₁₀ alkenyl, (C₃-C₈)cycloalkyl(C₂-C₁₀) alkenyl;

X is -O- or -S-;

5 R₂₁ is C₁-C₁₀ alkyl optionally substituted with 1 to 10 -F, -Cl or -Br,

C₂-C₁₀ alkyl substituted with 1 to 10 -OH, -CH₂-COOR₂₁₋₁ where R₂₁₋₁ is C₁-C₁₀ alkyl, C₃-C₈ cycloalkyl, C₃-C₈ cycloalkenyl, C₂-C₁₀ alkenyl containing 1 thru 4 double bonds optionally substituted with -OH, -F, -Cl or -Br,

10 -(CH₂)_{n1}-phenyl where n₁ is 0 or 1 and phenyl is optionally substituted with 1 thru 3 -F, -Cl, -Br, -OH, -OCH₃, -OC₂H₅, C₁-C₄ alkyl, -NH₂, -N(CH₃)₂, -N(C₂H₅)₂ or -NO₂,

-CH₂-CO-NR₂₁₋₂R₂₁₋₃ where R₂₁₋₂ and R₂₁₋₃ are the same or different and are -H, C₁-C₁₀ alkyl, C₃-C₈ cycloalkyl, -φ, -CH₂-φ and where R₂₁₋₂ and R₂₁₋₃ are taken together with the attached nitrogen atom to form a heterocyclic ring selected from the group consisting of 1-pyrrolidine, 1-piperidine, 1-piperazine and 1-morpholine,

15 6α-fluoro-17α,21-dihydroxy-16α-methylpregna-4,9(11)-diene-3,20-dione,

20 6α-fluoro-17α,21-dihydroxy-16α-methylpregna-4,9(11)-diene-3,20-dione 21-acetate,

25 6α-fluoro-17α,21-dihydroxy-16β-methylpregna-4,9(11)-diene-3,20-dione,

30 6α-fluoro-17α,21-dihydroxy-16β-methylpregna-4,9(11)-diene-3,20-dione 21-phosphonoxy,

hydrocortisone,

tetrahydrocortisol,

17α-hydroxyprogesterone,

11α-epihydrocortisone,

cortexolone,

corticosterone,

desoxycorticosterone,

dexamethasone,

35 cortisone 21-acetate,

hydr cortisone 21-ph sphate,

17α-hydroxy-6α-methylpregn-4-ene-3,20-dion 17-acetate.

7. A method of treating angiogenesis according to claim 1 where the angiostatic steroid is selected from the group consisting of $\Delta^{9(11)}$ -etianic esters of formula (IV) where

5 R_{10} is α - $R_{10-1}:\beta$ - R_{10-2} where R_{10-2} is -CH₃, R_{10-1} and R_5 taken together are -CH₂-CR₂-CR₃-CH- where R_2 is -H:-H and R_3 is -O,

R_6 is α - $R_{6-1}:\beta$ - R_{6-2} where R_{6-2} is -H and R_{6-1} is -H, -F and -CH₃,

R_7 is -H:-H,

10 R_{16} is α - $R_{16-1}:\beta$ - R_{16-2} where one of R_{16-1} and R_{16-2} is -H and the other of R_{16-1} and R_{16-2} is -CH₃,

R_{17} is C₁-C₄ alkyl or -(CF₂)_{n2}-CF₃ where n₂ is 0-3,

R_{21} is C₁-C₄ alkyl,

X is -O-;

15 20-substituted steroids of formula (I), where

R_4 is -H,

R_6 and R_9 are the same or different and are -H, -F, -Cl,

R_{11} is chosen from the group consisting of hydroxy and keto,

20 R_{20} is chosen from the group consisting of methoxy and thiomethyl, and

R_{17} is chosen from the group consisting of alkyl groups having less than 6 carbon atoms;

25 6 α -fluoro-17 α ,21-dihydroxy-16 α -methylpregna-4,9(11)-diene-3,20-dione 21-acetate,

6 α -fluoro-17 α ,21-dihydroxy-16 β -methylpregna-4,9(11)-diene-3,20-dione,

20 6 α -fluoro-17 α ,21-dihydroxy-16 β -methylpregna-4,9(11)-diene-3,20-dione 21-phosphonoxy,

30 hydrocortisone,

tetrahydrocortisol,

17 α -hydroxyprogesterone,

11 α -epihydrocortisone,

cortexolone,

35 corticosterone,

desoxycorticosterone,

dexamethasone,

cortisone 21-acetate,
hydrocortison 21-phosphate,
17 α -hydroxy-6 α -methylpregn-4-ene-3,20-dione 17-acetate,
6 α -fluoro-17 α ,21-dihydroxy-16 α -methylpregna-4,9(11)-diene-3,20-
5 dione.

8. A method of treating angiogenesis according to claim 1 where the angiostatic steroid is selected from the group consisting of
6 α -fluoro-17 α ,21-dihydroxy-16 α -methylpregna-4,9(11)-diene-3,20-
10 dione 21-acetate,
6 α -fluoro-17 α ,21-dihydroxy-16 β -methylpregna-4,9(11)-diene-3,20-
dione,
6 α -fluoro-17 α ,21-dihydroxy-16 β -methylpregna-4,9(11)-diene-3,20-
dione 21-phosphonoxy,
15 hydrocortisone,
tetrahydrocortisol,
17 α -hydroxyprogesterone,
11 α -epihydrocortisone,
cortexolone,
20 corticosterone,
desoxycorticosterone,
dexamethasone,
cortisone 21-acetate,
hydrocortisone 21-phosphate,
25 17 α -hydroxy-6 α -methylpregn-4-ene-3,20-dione 17-acetate,
6 α -fluoro-17 α ,21-dihydroxy-16 α -methylpregna-4,9(11)-diene-3,20-
dione.

9. A method of treating angiogenesis according to claim 1 where the
30 the route of administration of the suramin-type compounds is IV and
the route of administration of the angiostatic steroids is oral or
parenteral.

10. A method of treating angiogenesis according to claim 1 where the
35 the suramin-type compound and angiostatic steroid are not adminis-
tered in one dosage unit.

-30-

11. A method of treating angiogenesis according to claim 1 where the dose of the suramin-type compound is from about 1 to about 1000 mg/m²/day and the dose of angiostatic steroid is from about 0.1 to about 100 mg/kg/day.

5

12. A method of treating angiogenesis according to claim 1 where the treating angiogenesis is treating diseases of neovascularization.

13. A method of treating angiogenesis according to claim 12 where 10 neovascular diseases are selected from the group consisting of solid tumors, diabetes, arthritis, atherosclerosis, neovascularization of the eye, parasitic diseases, psoriasis, abnormal wound healing processes, hypertrophy following surgery, burns, injury, hair growth, ovulation and corpus luteum formation, implantation and embryo 15 development in the uterus.

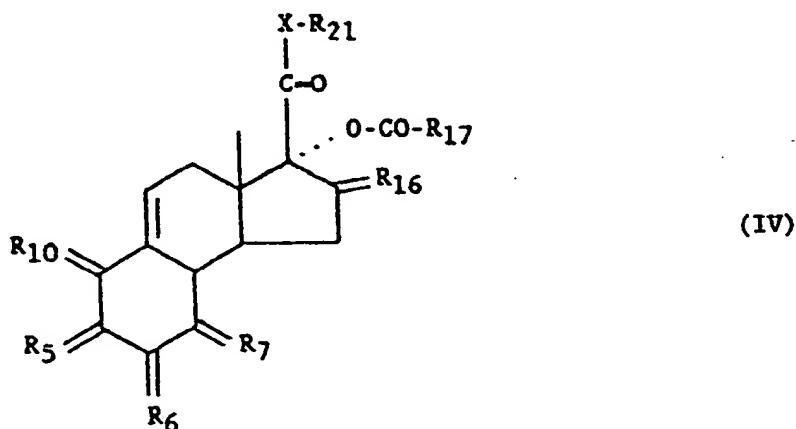
14. A method of treating angiogenesis according to claim 12 where the neovascular disease is solid tumors, diabetes, arthritis or psoriasis.

20

15. A $\Delta^9(11)$ -etianic ester of formula (IV)

25

30



where:

(A-I) R₁₀ is α -R₁₀₋₁: β -R₁₀₋₂ where R₁₀₋₂ is -CH₃, R₁₀₋₁ and R₅ taken together are -CH₂-CR₂-CR₃-CH- where R₂ is 35 α -R₂₋₁: β -R₂₋₂ where one of R₂₋₁ and R₂₋₂ is -H and the other of R₂₋₁ and R₂₋₂ is -H, -CH₃, -Cl or -F, where R₃ is -O or α -R₃₋₁: β -R₃₋₂ where one R₃₋₁ and R₃₋₂ is -H and the other of R₃₋₁ and R₃₋₂ is

-OR₃₋₃ where R₃₋₃ is -H, -PO(OH)₂ or -SO₃H;

(A-II) R₁₀ is α -R₁₀₋₃: β -R₁₀₋₄ where R₁₀₋₄ is -CH₃, R₁₀₋₃ and R₅ taken together are -CH=CH-CO-CH=;

(A-III) R₁₀ is α -R₁₀₋₅: β -R₁₀₋₆ and R₅ is α -R₅₋₅: β -R₅₋₆, where R₁₀₋₆ is -CH₃, one of R₅₋₅ and R₅₋₆ is -H and the other of R₅₋₅ and R₅₋₆ taken with R₁₀₋₅ is -CH₂-CR₂-CR₃-CH₂- where R₂ and R₃ are as defined above;

R₆ is α -R₆₋₁: β -R₆₋₂ where one of R₆₋₁ and R₆₋₂ is -H and the other of R₆₋₁ and R₆₋₂ is -H, -F, -Cl, -Br and -CH₃;

R₇ is α -R₇₋₁: β -R₇₋₂ where one of R₇₋₁ and R₇₋₂ is -H and the other of R₇₋₁ and R₇₋₂ is -H or -CH₃;

R₁₆ is -CH₂ or α -R₁₆₋₁: β -R₁₆₋₂ where one of R₁₆₋₁ and R₁₆₋₂ is -H and the other of R₁₆₋₁ and R₁₆₋₂ is -H, -CH₃, -OH or -F;

R₁₇ is C₁-C₂₀ alkyl, C₁-C₁₀ fluoroalkyl containing from 1-23 -F atoms, C₁-C₆ alkoxy, (C₁-C₈)alkylamino(C₁-C₆)alkyl, (C₅-C₇)cycloalkyl(C₁-C₆)alkyl, phenyl(C₁-C₆)alkyl optionally substituted with 1-3 -CH₃, -F, -Cl, -OH, -OCH₃, -OC₂H₅ and -NH₂, C₃-C₈ cycloalkyl, C₂-C₁₀ alkenyl, (C₃-C₈)cycloalkyl(C₂-C₁₀) alkenyl;

X is -O- or -S-;

R₂₁ is C₁-C₁₀ alkyl optionally substituted with 1 to 10 -F, -Cl or -Br,

C₂-C₁₀ alkyl substituted with 1 to 10 -OH, -CH₂-COOR₂₁₋₁ where R₂₁₋₁ is C₁-C₁₀ alkyl, C₃-C₈ cycloalkyl, C₃-C₈ cycloalkenyl, C₂-C₁₀ alkenyl containing 1 thru 4 double bonds optionally substituted with -OH, -F, -Cl or -Br,

-(CH₂)_{n1}-phenyl where n₁ is 0 or 1 and phenyl is optionally substituted with 1 thru 3 -F, -Cl, -Br, -OH, -OCH₃, -OC₂H₅, C₁-C₄ alkyl, -NH₂, -N(CH₃)₂, -N(C₂H₅)₂ or -NO₂,

-CH₂-CO-NR₂₁₋₂R₂₁₋₃ where R₂₁₋₂ and R₂₁₋₃ are the same or different and are -H, C₁-C₁₀ alkyl, C₃-C₈ cycloalkyl, - ϕ , -CH₂- ϕ and where R₂₁₋₂ and R₂₁₋₃ are taken together with the attached nitrogen atom to form a heterocyclic ring selected from the group consisting of 1-pyrrolidine, 1-piperidine, 1-piperazine and 1-morpholine.

16. A Δ ⁹⁽¹¹⁾-etianic ester of formula (IV) according to claim 15 where R₁₀ is α -R₁₀₋₁: β -R₁₀₋₂ where R₁₀₋₂ is -CH₃, R₁₀₋₁ and R₅ taken together are -CH₂-CR₂-CR₃-CH- where R₂ is -H:-H and R₃ is -O.

17. A $\Delta^9(11)$ -etianic ester of formula (IV) according to claim 15 where R_6 is α - $R_{6-1}:\beta$ - R_{6-2} where R_{6-2} is -H and R_{6-1} is -H, -F and - CH_3 .

5 18. A $\Delta^9(11)$ -etianic ester of formula (IV) according to claim 15 where R_{16} is α - $R_{16-1}:\beta$ - R_{16-2} where one of R_{16-1} and R_{16-2} is -H and the other of R_{16-1} and R_{16-2} is - CH_3 .

10 19. A $\Delta^9(11)$ -etianic ester of formula (IV) according to claim 15 where R_{17} is C_1-C_4 alkyl.

20. A $\Delta^9(11)$ -etianic ester of formula (IV) according to claim 15 where R_{17} is $-(CF_2)_{n_2}-CF_3$ where n_2 is 0-3.

15 21. A $\Delta^9(11)$ -etianic ester of formula (IV) according to claim 15 where R_{21} is C_1-C_4 alkyl.

20 22. A $\Delta^9(11)$ -etianic ester of formula (IV) according to claim 15 where X is -O-.

25 23. A $\Delta^9(11)$ -etianic ester of formula (IV) according to claim 15 where the $\Delta^9(11)$ -etianic ester is selected from the group consisting of

6 α -fluoro-17 α -hydroxy-16 α -methylandrosta-4,9(11)-dien-3-one 17 β -carboxylic acid methyl ester 17-acetate,

6 α -fluoro-17 α -hydroxy-16 α -methylandrosta-4,9(11)-dien-3-one 17 β -carboxylic acid methyl ester 17-trifluoroacetate,

6 α -fluoro-17 α -hydroxy-16 α -methylandrosta-4,9(11)-dien-3-one 17 β -carboxylic acid methyl ester 17-propionate,

30 6 α -fluoro-17 α -hydroxy-16 α -methylandrosta-4,9(11)-dien-3-one 17 β -carboxylic acid methyl ester 17-pentafluoropropionate,

6 α -fluoro-17 α -hydroxy-16 α -methylandrosta-4,9(11)-dien-3-one 17 β -carboxylic acid methyl ester 17-butyrate,

35 6 α -fluoro-17 α -hydroxy-16 β -methylandrosta-4,9(11)-dien-3-one 17 β -carboxylic acid methyl ester 17-propionate,

6 α -fluoro-17 α -hydroxy-16 β -methylandrosta-4,9(11)-dien-3-one 17 β -

-33-

carboxylic acid methyl ester 17-butyrate,

6 α -fluor-17 α -hydroxy-16 α -methylandrosta-1,4,9(11)-trien-3-one

17 β -carboxylic acid methyl ester 17-propionate,

6 α -fluoro-17 α -hydroxy-16 α -methylandrosta-1,4,9(11)-trien-3-one

5 17 β -carboxylic acid methyl ester 17-butyrate.

24. 6 α -Fluoro-17 α ,21-dihydroxy-16 α -methylpregna-4,9(11)-diene-3,20-dione.

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15

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US 90/02673

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all) *

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC⁵ : C 07 J 3/00, A 61 K 31/565

II. FIELDS SEARCHED

Minimum Documentation Searched ?

Classification System	Classification Symbols
IPC ⁵	C 07 J 3/00, A 61 K 31/00

Documentation Searched other than Minimum Documentation
to the Extent that such Documents are Included in the Fields Searched *

III. DOCUMENTS CONSIDERED TO BE RELEVANT⁶

Category *	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
X	EP, A, 0135476 (CIBA-GEIGY AG) 27 March 1985 see page 6, compound III; claim 8	15,17-19, 21-23
X	FR, A, 2369297 (CIBA GEIGY AG) 26 May 1978 see example 6	15,17-19, 21-23
X	EP, A, 0004772 (SYNTEX INC.) 17 October 1979 see page 33, lines 3-5	15,17-19, 21-23
X	CH, A, 634081 (CIBA-GEIGY AG) 14 January 1983 see the whole document	15,17-19, 21-23
		. / .

* Special categories of cited documents: ¹⁰

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the International filing date
- "I" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the International filing date but later than the priority date claimed

"T" later document published after the International filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"G" document member of the same patent family

IV. CERTIFICATE

Date of the Actual Completion of the International Search
14th August 1990

Date of Mailing of this International Search Report

19.09.90

International Searching Authority

EUROPEAN PATENT OFFICE

Signature of Authorized Officer

R.J. Eernisse

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages	Relevant to Claim No.
X	<p>Chemical Abstracts, vol. 58, 1963, (Columbus, Ohio, US), see abstract 11448b, & GB, A, 903049 (CHAS. PFIZER & CO., INC.) 9 August 1962</p> <p>---</p>	24
A	<p>Laboratory Investigation, vol. 59, no. 1, 1988, The United States and Canadian Academy of Pathology, Inc., (Washington, US), D. Ingber et al.: "Inhibition of angiogenesis through modulation of collagen metabolism", pages 44-51, see page 45, column 1, lines 10-23</p> <p>-----</p>	24

FURTHER INFORMATION CONTINUED FR M THE SEC ND SHEET

V. OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE¹

This International search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. Claim numbers 1-14, because they relate to subject matter not required to be searched by this Authority, namely:

See PCT-Rule 39.1.(iv): methods for treatment of the human or animal body by surgery or therapy as well as diagnostic methods.

2. Claim numbers, because they relate to parts of the International application that do not comply with the prescribed requirements to such an extent that no meaningful International search can be carried out, specifically:

3. Claim numbers....., because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING²

This International Searching Authority found multiple inventions in this International application as follows:

1. As all required additional search fees were timely paid by the applicant, this International search report covers all searchable claims of the International application.

2. As only some of the required additional search fees were timely paid by the applicant, this International search report covers only those claims of the International application for which fees were paid, specifically claims:

3. No required additional search fees were timely paid by the applicant. Consequently, this International search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

The additional search fees were accompanied by applicant's protest.
 No protest accompanied the payment of additional search fees.

**ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO.**

US 9002673
SA 37148

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 17/09/90. The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

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